

Decision Memo for Warm-Up Wound Therapy® a/k/a Noncontact Normothermic Wound Therapy (NNWT) (CAG-00114N)

Decision Summary

Medicare has decided to issue a national noncoverage policy for all uses of noncontact normothermic wound therapy for the treatment of wounds, because the medical literature is not sufficient to support a national coverage determination.

It is our intention to publish a noncoverage policy in the Coverage Issues Manual.

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Decision Memo

To: Administrative File CAG: (#CAG-00114N)
Noncontact Normothermic Wound Therapy (NNWT)

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Subject: Coverage Decision Memorandum for Noncontact Normothermic Wound Therapy
Date: January 14, 2002 (amended February 14, 2002)

This memorandum serves four purposes: (1) describes the pathophysiology and standard treatment of pressure ulcers, venous stasis ulcers, diabetic peripheral ulcers, complicated or non-healing surgical incisions/wounds and chronic wounds; (2) describes the NNWT device; (3) analyzes relevant clinical literature on the use of NNWT in each of the aforementioned wound types; and (4) delineates the reasons supporting national noncoverage of NNWT in treating these five wound types.

I. Clinical Background

In the United States, there are annually 6.5 million chronic wounds. Wound care consists of interventions to control infection and enhance healing, such as, the use of antibiotics, gels, fillers, powders and other applications to control infection, such as, mechanical debridement of necrotic tissue, and the application of various protective dressings.

A wound is any interruption in the continuity of the body surface and can range from a simple scratch to an interruption that goes through tissue and muscle down to bone. Generally wounds heal in an orderly fashion, first by reestablishing epithelial integrity, then by laying down new collagen to strengthen the damaged tissue. The result is re-establishment of anatomic and functional integrity.

A wound is a disruption of normal anatomic structure and function. Acute wounds are wounds of relatively new onset that are proceeding through an orderly and timely reparative process resulting in restoration of anatomic and functional integrity.¹ Fortunately, most wounds are acute wounds that heal rapidly and uneventfully. In chronic wounds, the healing process is disrupted by some underlying abnormality that prolongs the inflammatory phase, resulting in poor anatomic and functional outcome. Wounds are categorized as acute or chronic based on the timeliness of healing. Non-healing chronic wounds result when tissues fail to heal following traumatic injury, surgical procedures, or metabolic, neoplastic or infectious disorders.

There are various types of wounds: pressure ulcers, venous stasis ulcers, diabetic peripheral ulcers, arterial ulcers, surgical wounds, and traumatic wounds are some of the more common examples. Since the etiology of wounds vary, the most effective therapy may vary as well. For example, the etiology of a pressure ulcer relates to unrelieved pressure on the skin, whereas the etiology of a diabetic ulcer, and subsequent recovery from, is related to vascular problems. Therefore, it is difficult to generalize the findings from studies on therapy from one type of ulcer to another type. According to the "Guidance for Industry-Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment," the Food and Drug Administration (FDA) states that "Wounds differ pathophysiologically, making it difficult-if not impossible-to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type. Separate safety and efficacy data should be submitted for each wound type for which an indication is sought."²

Wound care must be directed at providing an environment in which the body can effectively carry out the healing process. Early concepts in wound management involved soaking the wound in antiseptics to kill bacteria and then covering the wound with a dry dressing. As the biology of wound healing has become better understood, a variety of wound care strategies and products have been developed to help aid the healing process. Various new dressings such as alginates, hydrogels, films, and foam products are now used. Additionally, newer techniques such as negative pressure dressings, growth factors, and radiant heat are also being investigated.

The multitude of wound care regimens belies the complexity of wound care management and the lack of one, universally proven treatment strategy. Knowledge of the pathophysiology of healing combined with realistic patient outcomes will help guide the clinician in choosing the wound care treatment plan. Lait and Smith reported that no single wound dressing is sufficient for all types of wounds, and few are ideally suited for the treatment of a single wound through all phases of healing³. The ideal dressing is described as one that provides a moist environment, is comfortable, removes necrotic debris and stimulates the formation of granulation tissue and re-epithelialization.⁴ In this decision memorandum, six different types of wounds will be addressed: pressure ulcers, venous ulcers, diabetic/neuropathic wounds, complicated or non-healing surgical incisions/wounds, and chronic wounds whether or not falling into one of the aforementioned categories.

Pressure ulcers, also known as decubitus ulcers or bedsores, can be a common and costly problem, particularly among the elderly, in acute care, nursing home, and home care populations. A pressure ulcer is any lesion caused by unrelieved pressure that results in damage to underlying tissue. Pressure ulcers occur when pressure or shear forces on the skin lead to occlusion of capillary blood flow and, ultimately, to skin cell death. Capillary occlusion primarily affects areas of the skin that are compressed against the underlying bone when an individual sits or lies down. The skin of an immobile bedridden patient is more likely to be affected by pressure and shear and the resulting damage usually occurs over a bony prominence. Deep tissue necrosis and a loss of volume are characteristic of these ulcers. The most common areas for the development of pressure ulcers are on the buttocks (sacral areas), hips (iliac crest), knees, heels and ankles.⁵

Pressure ulcers are generally classified by stages. Stage I pressure ulcers present as non-blanching erythema with intact skin. Stage II ulcers involve a partial thickness loss involving the epidermis or dermis. Stage III ulcers are full thickness and extend down to, but not through, the underlying fascia. Stage IV ulcers involve tissue below the fascia, exposing muscle and even bone.

Pressure ulcers generally occur in people who have poor mobility or are bedridden, such as patients in intensive care units and people with neurologic problems. Prevention of pressure ulcers involves frequent repositioning of the patient, keeping the surrounding skin dry and clean (i.e. free of feces and urine), and, in some cases, using various support surfaces that keep a person's weight evenly distributed. Once these wounds develop, moist dressings, frequent turning to relieve pressure, and good hygiene are standard therapies. Unfortunately, the underlying immobility and difficulty relieving surface pressure points makes treating these wounds a challenge.

Venous ulcers usually occur in the lower extremities. They result from venous obstruction or valvular incompetence. The subsequent venous hypertension then affects the vascular supply to surrounding tissue, resulting in tissue hypoxia and ulcer formation. Because the underlying pathophysiology is venous insufficiency, the treatment of venous ulcers is directed on two fronts - correction of the underlying venous incompetence and wound care. Moist dressings combined with compressive bandage systems are usually effective in healing these ulcers, although the time to heal may be prolonged in some patients. Failure to respond to conventional therapy occurs in some individuals, and may lead to ulcers that are present for years.

Diabetic ulcers are thought to develop from the combination of small vessel disease, which affects tissue perfusion, and peripheral neuropathy, which leads to a loss of protective sensation. Injuries in these patients are often slow to heal, and might go unnoticed by the patient due to absence of sensation. In addition, many diabetics have peripheral vascular disease that further compromises blood flow and tissue oxygenation. Foot ulcers are a major health problem for diabetics. It is estimated that up to 15% of diabetics will develop a foot ulcer at some time in their life, and approximately 70% of such patients develop recurrent ulcers⁶. Diabetic foot ulcers precede approximately 85% of lower limb amputations⁷. Educating diabetics about routine foot care and self-examination can help to prevent foot ulcers. Once established, however, these ulcers can be slow to heal even with the best conventional therapies. Moist dressings, debridement and off-loading are the mainstays of treatment.

Surgical wounds are iatrogenic, and heal by either primary or secondary intention. Primary intention occurs when the wound edges are approximated (i.e. sutured or stapled). Secondary intention occurs when the wound is left open to granulate in on its own. Healing by secondary intention is generally chosen for infected or contaminated wounds. Standard treatment of these wounds includes moist dressings, debridement, plus local and systemic antibiotics as needed.

Noncontact Normothermic Wound Therapy (NNWT): NNWT is a device that utilizes radiant heat to promote wound healing. The requestor stated the device's effect is based on the premise that wounds are hypothermic relative to normal body temperature and that by increasing them to normal body temperature will promote healing. The device consists of a wound cover, warming card, temperature control unit and A/C adapter and power cord (Figure 1).

The wound cover is dome-shaped. It consists of a clear polyester pocket for holding the infrared warming card, a clear polyurethane top window for viewing the wound, a flexible polyurethane transition portion to accommodate patient movement, a hydrophilic foam inner ring for absorbing wound fluid and an adhesive border for attaching to surrounding skin. The warming card is flat and rectangular, and is made of an aluminized polyester thermal insulation layer, a metal foil heater circuit layer, and two temperature sensors with an attached electrical cable. The temperature control unit contains the heat control and safety circuitry as well as a rechargeable battery pack. The A/C adapter and power cord allow the device to be used while the battery pack is being recharged.

CMS notes that, as compared to standard wound care regimens, this therapy also differs in the non-contact nature of the bandage. This sealed wound cover provides a moist, humid environment and reduces mechanical disturbance of the wound surface that is encountered with standard dressings. Thus, the device has two unique features, radiant heat and non-contact structure, that could contribute to any impact on outcome.

II. History of Medicare's Coverage on NNWT and Timeline of Recent Activities

Section 2079 of the Medicare Carriers Manual states that primary and secondary dressings are covered when required for the treatment of a wound caused by, or treated by, a surgical procedure that has been performed by a physician or other health care professional to the extent permissible under state law. Devices for wound care may be covered under the Durable Medical Equipment benefit as defined in Section 1861(n) of the Social Security Act.

Current CIM Policy: Currently there is no CIM policy on NNWT.

Benefit Category Determination: The benefit category for NNWT is durable medical equipment.

Timeline of Recent Activities:

August 23, 2001 CMS met with representatives of Augustine Medical, Inc., manufacturers of WarmUp™ (the only NNWT device on the market). At this meeting they submitted a formal request for consideration of coverage for NNWT.

The company requested coverage for use of this device in five types of wounds:

- Pressure ulcers
- Venous stasis ulcers
- Diabetic/Neuropathic ulcers
- Complicated or non-healing surgical incisions/wounds
- Chronic wounds, whether or not falling into one of the foregoing categories

September 6, 2001 CMS sent questions to Augustine Medical on September 6, 2001 to facilitate completion of their request. Specifically, CMS asked the company to confirm their desire to request coverage for all five wound types despite lack of studies for several of these wound types.

October 2, 2001 CMS accepted the request for a national coverage determination after reviewing the scientific literature and additional information provided on the different types of wounds for which the company is requesting coverage. Due date posted as January 2, 2002

December 26, 2001 Request for withdrawal of coverage request received from Augustine Medical.

III. FDA Status

The Food and Drug Administration (FDA) granted Augustine Medical, Inc. clearance to market their NNWT device on March 28, 1997. This clearance was through the 510(k) process meaning that NNWT was considered substantially equivalent to predicate device(s) marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendment of the Federal Food, Drug and Cosmetic Act. The predicate devices to which NNWT was compared were ClearSite™ wound dressing, Lyofoam™ wound dressing, and Seabrook MicroTemp™ pump and pads. No clinical data regarding impact of NNWT on wound healing was requested by or provided to the FDA. The FDA stated that the intended use was for local management of wounds including venous, arterial, diabetic and pressure ulcers. The FDA specifically stated in a letter to the manufacturer (dated March 28, 1997) that the marketing of the device was subject to the following limitations:

1. This device may not be labeled for use on third degree burns.
2. This device may not be labeled as having any accelerating effect on the rate of wound healing or epithelialization.
3. This device may not be labeled as a long-term, permanent, or no change dressing, or as an artificial (synthetic) skin.
4. This device may not be labeled as a treatment or cure for any type of wound.

IV. General Methodological Principles of Clinical Study Design

When making national coverage NCDs, we evaluate relevant trials to determine whether or not the data is of sufficient quality to support a finding of clinical effectiveness. It has been our experience that many studies performed to evaluate wound treatments are of poor quality. CMS considers several generally accepted methodological principles when assessing a clinical trial. For example, we evaluate whether or not general methods of study design have been followed, such as calculating sample size *a priori*, specifying inclusion and exclusion criteria, describing the process for the selection of study participants and the ways in which the consistency of this process was maintained, ensuring comparability of experimental and control groups at baseline to the extent possible, describing baseline characteristics of the participants, randomizing study subjects, masking of patients and investigators to the therapy administered to the extent feasible, describing co-interventions in detail, and performing appropriate statistical analyses, such as statistical tests of differences in baseline characteristics between the comparison groups. CMS evaluates other study design issues, which, in the case of wound care trials, include, among other things, the following:

- Has an appropriate outcome been used? For example, the optimal outcome to measure is the number and proportion of wounds that reach complete closure. Assessing partial healing provides less assurance of clinical effectiveness, because the clinical benefit of partial healing has not been demonstrated.
- Have appropriate measures of endpoints been selected, identified prior to initiating the trial, and standardized across all study sites? Have clear measurement criteria been provided? Has the process used to measure the selected outcomes and methods in which the study investigators insured the consistency of this process across different study sites been described?
- Was the appropriate patient population studied? For example, was the study performed on patients with the wound type for which coverage is sought?
- Has a single reference wound been selected for each patient? Generally, including multiple wounds on a single patient in the analysis provides limited additional data of value, because individual wounds are not independent.
- Have all subjects, regardless of the protocol arm to which they are assigned (e.g., investigational treatment, control), received good standard care and the same standard care procedures? Have the standard care procedures been described in detail?
- Have variables that may affect results been addressed in the analysis, including surface area, depth, and chronicity of wounds, condition of the subject, age of the subject?
- Has the effect of the therapy under investigation on the wound been evaluated? Adverse effects on healing can manifest in several ways, including tissue necrosis requiring more debridement, erythema, and discharge.
- Have adequate follow-up evaluations been performed? Clinical benefits from wound therapies can be short-lived and, therefore, of limited clinical value.

The FDA has also issued guidance that may be useful to investigators.⁸ In addition, numerous useful texts have been published on general trial design and evidence-based medicine review of studies.⁹

V. Summary of Evidence

CMS sought clinical articles (e.g., randomized and non-randomized clinical trials and clinical series) that were published, accepted for publication or submitted for publication in peer-reviewed journals. Only English language articles were considered. Abstracts were excluded because of lack of sufficiently detailed information on study design and detailed discussion of results. Case reports and non-clinical studies (i.e., in vitro, animal, meta-analysis and cost-effectiveness studies) were excluded from this review. In addition, because none of the wound types described is rare, and because there is evidence that suggests that not all respond to the same standard therapy, per the FDA Guidance document,¹⁰ CMS looked at each of the five wound types separately, and required evidence on each wound type in considering its decision.

The requestor submitted 33 references. The bibliography of each of these references was reviewed to identify any additional relevant articles. In addition, a Medline search (using the keywords wound, normothermic, heat, chronic, nonhealing, and noncontact) was performed. These measures did not reveal any relevant articles in addition to the 33 the requestor provided. The following is a description of the 33 articles:

- 10 randomized controlled clinical trials (RCT) - Five were included in this review (Alvarez (submitted for publication), Price 2000, McCulloch (publication pending), Santilli 1999, Whitney 2001). The remaining five were excluded for the following reasons: two did not address the use of NNWT in treating one of the requested wound types (Melling 2001, Plattner 2000), two were abstracts (Farac 1999, Santilli 1998) for which full publications never subsequently appeared, and one (Kloth, submitted for publication) contained incomplete information.
- 4 non-randomized clinical trials - One was included in this review (Kloth 2000). Reasons for excluding the other three were: two did not address the use of NNWT for one of the five wound types (Ikeda 1998, West 1996); one was an abstract (Manor-Care® study).
- 2 case series - Both were included in this review (Cherry 1999, Karr (publication pending)).
- 8 case reports - All were excluded (Cuttino, Edvalson, Stanfield (2 case reports), Swartz (2 case reports), and Taylor (2 case reports). (all 8 were unpublished)

- 5 in vitro studies - All were excluded (Park 1998, Park (2 that are pending publication), Tang (publication pending) and Zhido 2000).
- 2 animal studies - Both were excluded (Lee 2000, Tretinyak (non-published)).
- 1 meta-analysis of NNWT literature - (Mahoney, publication pending). It was included but it only contained studies that we had otherwise reviewed.
- 1 cost-effectiveness study of NNWT - Excluded (Macario, publication pending).

A total of eight articles (Alvarez (publication pending), Cherry 1999, Karr (publication pending), Kloth 2000, McCulloch (publication pending), Price 2000, Santilli 2000, Whitney 2001) were identified which met the prescribed eligibility criteria. They are summarized in this decision memorandum.

Pressure Ulcers

Three studies investigated the use of NNWT in treating pressure ulcers (Kloth 2000, Price 2000, Whitney, 2001). Price and Whitney's studies were randomized controlled clinical trials. The study by Kloth is reported to be a non-randomized controlled study, however, the controls were historical and many potential treatment biases exist. Therefore, it is more appropriate to characterize this article as a case series.

Price et al enrolled 58 patients with either Stage III or IV pressure ulcers to receive either NNWT therapy or standard therapy. In the NNWT group, the bandage was left on at all times (except for daily dressing changes), and the wound was heated twice daily for one-hour periods. Heating was done in the morning and evening; the authors do not state what the time between heating intervals was nor if this was a consistent interval. The control group received routine care with absorbent dressings. The authors do not go into detail on the type of standard care provided nor do they state what the nursing care was for either group of patients (i.e., type of bed used, frequency of turning, hygiene). The study continued for six weeks or until healing occurred, whichever came first. "Healing" was not defined. Subjects were considered "evaluable" if they remained in the study for three weeks.

Fifty patients were followed for the requisite three weeks, and their data were considered "evaluable." Of the eight patients that were not followed for three weeks, seven came from the NNWT group. The reasons for withdrawal included death (three patients), general deterioration in medical condition (three patients), patient wished to withdraw (one patient), and allergy to the NNWT adhesive (one patient). Of the 50 evaluable patients, 43 had Stage III ulcers and 7 had Stage IV ulcers. The patient care setting ranged from home to hospital and the authors do not provide information on how many patients were in each of these settings. The final tally was 25 patients in the NNWT group and 25 in the control group.

Weekly assessment by one of two wound care nurses was done in a masked fashion. No information was given on how they were able to ensure the observers were masked. After six weeks, the number of "healed" ulcers was approximately the same in each group: 3 in the NNWT group and 2 in the control group (no p value given). The mean area of wound reduction was also not statistically different in either group ($p=0.078$). In addition, pain, which was analyzed in each patient using a visual analogue scale, was no different in either group (no p value given).

The authors did, however, use a Kaplan Meier Survival analysis to investigate the time to achieve a reduction to 75%, 50% and 25% of original wound area. They found that there was a difference in the time to reduce the wound to 50% ($p=0.039$) and 25% ($p=0.011$) of its original area with the NNWT group achieving these markers faster than the control group. However, there was no difference in time to reduce the wound to 75% of its original area ($p=0.057$).

Whitney, et al. studied 40 patients with pressure ulcers. They recruited their subjects through public service announcements, home health care agencies, and long-term care facilities. Patients were randomized into one of two arms: NNWT or conventional wound therapy. The study was conducted in both the home and institutional setting.

Patients in the NNWT group wore the noncontact bandage at all times except for daily bandage changes. The wounds in the treatment group were heated daily for one-hour periods. Heating was done every six to eight hours for a total of three episodes per day. The subjects in the control group received conventional wound therapy. While they defined the dressings used in standard care, the ancillary care (i.e., turning, nutrition) were not defined. The study was carried out for eight weeks, or until the wound healed, whichever came first. The authors did not state what the criteria were for deciding a wound was healed. Wounds were assessed weekly, it was not stated whether the observers were masked to the treatment group, and change in wound status was measured by linear healing rate. The authors reported this data in centimeters per day. This inconsistency (cm/day when measurements were done weekly) was not discussed.

Eleven patients withdrew from the study for the following reasons: eight because of non-adherence to the study protocol, one because of infection unrelated to the study, one due to provider decision to change therapy, and one because of periwound damage due to bandage. Six of the withdrawals were in the control arm and five were in the NNWT group.

The authors stated that there were no statistically significant differences between the groups in regards to demographic or wound characteristics (no p values provided). However, more patients in the control group used a regular mattress as a support surface as compared to the NNWT group (eight patients vs. four patients). In addition, there is no discussion of the supporting care (e.g., turning, off-loading, hygiene) each group received.

The authors found that the linear rate of healing was faster in the NNWT group (0.012 cm/day) when compared to the control group ($p=0.004$ cm/day, $p=0.01$). At the end of the eight week period, 71% of Stage III ulcers treated with NNWT vs. 53% of Stage III ulcers in the control group had completely healed. The authors did not give the actual numbers of completely healed wounds, nor do they give significance information on the difference in complete healing.

The study by Kloth et al also investigated NNWT use in pressure ulcers. This study included 14 patients with pressure ulcers (7 with Stage III wounds and 7 with Stage IV wounds). These patients came from the geriatric unit (n=7) at a Veterans Administration hospital and from the spinal cord unit (n=7) at the same hospital. The authors stated they used six patients as retrospective controls. This group was made up of patients who had served as controls for a previous study. While the authors provided information on standard care given to the NNWT group, it is unclear if this was the standard care their historical control group received. It is also unclear how long the historical control group was followed. In addition, the method of selecting patients for the NNWT treatment arm was not stated. The authors' stated that the six subjects who made up the retrospective controls were "carefully selected," though the criteria for selection of historic controls was not further described.

The 14 study patients were treated with NNWT Monday through Friday for two one-hour periods per day. Treatments were done for four consecutive weeks. The noncontact bandage was left on the wound only for 4.5 hours per day. These wounds received standard care the remainder of the time.

The mean age of the patients in the geriatric unit was 63 years and the mean age of the patients in the spinal cord unit was 58 years (median ages were 70 and 61 years respectively). No statistical comparison historic control of baseline characteristics was provided. The authors stated that the NNWT wounds decreased in size by 60.7% over the four-week study period, whereas wounds in the control group had decreased by only 19.24% over a four-week period ($p<0.05$). Again, these were retrospective controls and any interpretation of this data must take this into account.

Venous Ulcers

Three studies investigating the use of NNWT in venous stasis ulcers were identified (Cherry 1999, Santilli 1998, Santilli 1999). The Cherry study was a case series involving five patients who had a lower extremity venous ulcer for a mean duration of eight months prior to the study (range 3 - 13 months). The five patients received NNWT therapy three times a day for periods of one-hour. Each one-hour warming episode was separated by a one-hour "rest" period in which the bandage was left in place but the heating element was turned off. After the three warming episodes were completed each day, the noncontact bandage was removed and a compression stocking was put in place. Warming therapy was carried out for two weeks. The patients were followed for a total of 12 weeks.

By the end of the 12 weeks, four of the patients' ulcers healed. The authors did not state how healing was defined nor did they provide a statistical comparison of baseline data on ulcer size. In addition, they stated that all patients reported a decrease in pain with the institution of NNWT, but do not discuss how pain was assessed.

In the Cherry study, the type of compression stocking being used prior to NNWT was changed in all five patients with the institution of warming therapy. Thus, the study involved two interventional changes: institution of warming therapy and a change in compression stocking. This is potentially significant because the four patients whose ulcers healed all were switched to Jobst stockings, while the one patient that did not heal was using another stocking. Thus, it is unclear whether the healing was aided by the warming therapy or by the change in compression technique.

The study by Santilli et al (1999) involved 17 patients with 31 venous ulcers. This was a prospective study conducted in the setting of a Veterans Administration Hospital and the patients served as their own historical controls. The method of selecting patients for this study (i.e. patient recruitment) was not defined. The average age of the patients was 68 years (\pm 12.6 years) and 82% (14/17) were male. The average wound duration prior to the study was 4.44 \pm 6.2 years (range 16 weeks to 20 years). The stage of the wounds at baseline was not stated. Five of the 17 (29%) subjects had a history of smoking (not stated if current or past use) and 7/17 (41%) of the subjects were diabetic (level of control and type of diabetes not stated).

Patients in this study underwent NNWT use for two weeks. During this period, the wounds were heated for a total of three hours per day alternating with one-hour periods of non-heating. After the daily warming periods were complete, the device was removed and the wounds dressed with saline soaked gauze and compression stockings (type used not stated). The authors stated that after discharge the patients were treated with Unna boots and followed weekly. The temporal relation of discharge to the completion of the two-week NNWT trial and the total length of follow-up was not stated.

During the two weeks of in-patient NNWT use the average wound size decreased from $21.6 \pm 45.8 \text{ cm}^2$ to $12.1 \pm 27.3 \text{ cm}^2$ ($p=0.0024$). The authors also assessed the patients' pain level using a visual analogue scale and the pain score improved from 3.2 ± 2.5 to 0.9 ± 3.2 ($p=0.0051$). Following discharge, 8/17 (47%) of the patients had complete healing within 12 weeks. The authors reported that diabetes and smoking had no effect on wound healing in their patients.

Diabetic/Neuropathic Ulcers

Two studies were identified that specifically addressed the use of NNWT in the treatment of diabetic peripheral ulcers (Alvarez, publication pending, and McCulloch, publication pending). The manufacturer submitted a third article that they felt supported NNWT for this indication (Karr, publication pending). The design of the Karr study, as will be described in detail, was not specifically intended to investigate the healing of typical diabetic ulcers.

In the McCulloch study, 40 patients with diabetic, neuropathic foot ulcers were divided into two groups with equal numbers receiving NNWT and standard wound care. While the authors stated this was done in a random fashion, their method of randomization involved an initial coin toss. They decided that if the toss resulted in "heads" the first patient would be assigned to the warming group and then all subsequent patients would be assigned to groups in an alternating fashion. This however is not true randomization since there is potential for the person enrolling patients to know to which group each consecutive patient would be assigned.

Patients in the NNWT group were instructed in the application of the device. The wounds were heated for a total of two hours per day (Monday through Friday) alternating with a one-hour period of non-heating. Following the two warming periods, the patients removed the device and dressed their wounds with standard dressings and applied off-loading devices. The authors stated that the wound cover could not be used in conjunction with the off-loading devices and, thus, had to be removed. The control group was treated with standard dressings and off-loading devices in a similar manner as used for the NNWT group.

The study does not state in what setting this was performed (i.e. institutional or home). The method of patient selection is also not defined (i.e., patient recruitment). The study was conducted for eight weeks, or until the wounds healed, whichever came first. All subjects underwent a weekly assessment in the clinic. It is not stated who assessed the wounds or whether this person was masked to treatment group. The rate of wound healing was used to assess wound change.

Of the 40 patients, 4 were dropped from the study for "non-study related issues" (two in each group). The reasons for removal were not stated. The baseline surface area measurements for the wounds were: controls = $2.58 \pm 2.89 \text{ cm}^2$ and NNWT = $2.02 \pm 1.53 \text{ cm}^2$. This was not statistically different ($p < 0.46$).

The mean healing rate for the NNWT group was $0.019 \pm 0.019 \text{ cm}^2/\text{day}$ as compared to the control group whose healing rate was $0.008 \pm 0.009 \text{ cm}^2/\text{day}$ ($p < 0.05$). Additionally, 13/18 (72%) wounds in the NNWT group healed within the 8 weeks of the study while only 5/18 (28%) wounds in the control group healed in the same time frame ($p < 0.05$).

Alvarez also investigated NNWT in diabetic foot ulcers. Ten patients were randomly assigned to receive NNWT and 10 were randomly assigned to standard wound care. The study was conducted over a 12-week period. Patients maintained their assigned bandage group until the 12-week time-point, unless they healed before then, in which case the bandage was discontinued. The authors defined healing as full epithelialization of the wound bed with no drainage. The authors stated that the patients' characteristics were not significantly different between the treated and control groups (p values not given). Patients in the NNWT group kept their noncontact bandage on at all times and had the wound heated three times per day for one-hour periods. The control group had daily wet-to-dry dressing changes. Both groups received the same type of off-loading.

Wounds were clinically assessed weekly, and the rates of wound healing were computed each week. In addition, the number of wounds healed at the end of the 12-week period was tallied. They provided rates and p values for healing at 2-week intervals (i.e. weeks 2, 4, 6, 8, 10, and 12). At no point was the rate significantly faster for NNWT (see evidence table). At the end of 12 weeks, the authors reported that 70% of the wounds in the NNWT group were healed vs. 40% in the control group. The authors did not give the actual numbers of healed wounds nor did they report the p value for this difference.

The study by Karr was designed to investigate the effect of NNWT on the healing of ulcers overlying osteomyelitis. In this study there were 10 patients assigned in a non-random manner to receive NNWT and there were 3 controls. While 9 patients in the NNWT group and 2 in the control group had either insulin or non-insulin dependent diabetes, the wounds described are not typical diabetic peripheral ulcers. The study does not define patient selection (i.e., patient recruitment), treatment protocols, or method of wound assessment (i.e. single/multiple evaluator, masking, technique used to measure wounds). They reported that NNWT treated wound healed in an average of 97 days while control subjects took an average of 139 days to heal.

Complicated or Non-Healing Surgical Incisions/Wounds

No articles were identified which addressed the use of NNWT in conjunction with these types of wounds.

Chronic Wounds, Whether or Not Falling Into One of The Foregoing Categories

No articles were identified which addressed the use of NNWT in conjunction with these types of wounds.

VI. Analysis

For centuries wounds have been treated with heat; the theory being that heat leads to vasodilation of local vessels, which in turn delivers oxygen to the wound. It is the delivery of heat to a wound that the requestor states is the principal benefit provided by the NNWT device. The requestor states that all skin is hypothermic relative to core body temperature, that hypothermia is a primary inhibitor of wound healing, and that hypothermia is the reason wounds become chronic. The NNWT device, they hypothesize, reverses this hypothermia, and, therefore, is unique in its ability to promote wound healing.

The requestor also indicated that the noncontact design on the wound cover is an important feature. The design of this dressing is such that it does not transmit mechanical trauma to the wound bed, drains off wound exudate, and provides a humid environment. There is indirect evidence that such features are beneficial for wounds. In vitro studies have demonstrated that chronic wound fluid inhibits the growth of fibroblasts^{11,12}. Also, a humid, moist environment helps to prevent desiccation of new cells and enhances epidermal migration^{13,14}.

The NNWT device, therefore, introduces two potential benefits to aid in wound healing: a non-contact dressing that produces a humid environment while also wicking away wound fluid, and a method of directing radiant heat in a controlled fashion to the wound bed. It is important that any study investigating the use of NNWT be designed so that an understanding of which of these features (e.g., a noncontact, sealed chamber and/or radiant heat) produces any observed benefit. A useful approach would be studies with three arms: 1) a group receiving NNWT warming therapy, 2) a sham treatment group that had the NNWT wound cover placed over the wound but without active heating, and 3) control group who received standard, well defined wound care. All other aspects, including nursing care, should be similar between the three groups. That would help limit the biases that make interpreting results difficult.

In a study by Plattner et al¹⁵, the authors placed NNWT devices over the abdominal wounds of patients who had undergone elective surgery. They were attempting to see if warming increased the subcutaneous oxygen pressure. They found that simply placing the non-contact bandage over the wound increased tissue oxygen pressure significantly over baseline. While tissue oxygen levels increased further with heating, the incremental clinical benefit of these increases was not confirmed. In addition, Kloth¹⁶ investigated NNWT in pressure ulcers and noted that wound surface temperature increased 0.8 degrees simply with the placement of the wound cover. Whitney¹⁷ stated, "The result of our study and similar findings of others supports the need for additional larger, controlled multisite trials. Because of the noncontact feature of this wound therapy bandage, inclusion of subjects treated with the dressing but without warming should be included if possible." These three studies support our position that a sham treatment group, one in which the dome cover is placed over the wound but not actively heated, is needed in future studies. It is possible that the wound cover, and its sealed humid environment, produces part or all of the beneficial effect. If that is the case, then the need for additional heating is unclear, and that would substantially alter this therapy.

A study by Rabkin and Hunt¹⁸ investigated the relationship between locally applied heat and subcutaneous blood flow and oxygen tension. They used a warm moist towel in a sealed plastic wrap to warm the skin, and found an increase in skin oxygen levels with heating. This leads us to ask if heating alone could aid wound healing. The studies reviewed demonstrated that the NNWT device raised surface temperatures approximately 2 - 3 degrees. It would be useful to know if other, less involved methods for increasing local skin temperature had any effect on wound healing. For instance, could a heating pad placed on a low setting or an extra blanket applied for intermittent periods be useful?

In addition, it is preferable when reviewing studies that the methods for use of a device and the measurements used to assess wound change across studies comparable to assess whether or not reported results are consistent. Some of the reviewed studies directed patients to wear the NNWT device at all times while other studies had patients wear the NNWT bandage part of the time and a conventional bandage at other times. Methods of assessing the wounds varied. Some investigators used linear healing rate, others used change in wound surface area, and others discussed time to when the wound had healed completely. These variable benchmarks were not always well defined by the investigators at the outset. In addition, there is disagreement as to what is the most appropriate method to assess wound healing. Some investigators argue that because wounds do not heal at a linear rate, wound healing should be modeled as an exponential decay function.¹⁹ Finally, wound healing often takes longer periods to affect than what many of these studies allow for follow-up. Additional studies should be both longer and provide multiple measures of wound healing to allow for a more realistic, clinical-setting experience.

Overall none of the studies reviewed were of a high quality study design. While many of the studies give a report of beneficial effect from the NNWT, their methodologic shortcomings make drawing positive conclusions about the device difficult. A review of each group of articles based on wound type follows. In assessing each article, major flaws that seriously limited the ability to draw conclusions from the study are stated. If there were additional, less serious flaws, these are noted as well.

Pressure Ulcers

The study by Kloth et al suffered from two major flaws, lack of a true comparison group, and failure to prospectively define what the endpoint in wound assessment was. The authors described this study as a controlled non-randomized trial. However, the controls were retrospective, and there was limited information provided on their selection and treatment. Thus, a more accurate description of this study design would be that it is a case series. Lack of a true comparison group limits the ability to make any inference about the effectiveness of the treatment. In addition, the study provided no information on what the measured wound endpoints were. While they stated that wounds treated with NNWT had a larger percentage decrease in wound size as compared to their "controls," the aforementioned problems with their control group make the validity of this statement questionable.

Less serious flaws with the Kloth study included the sample size. Their cohort of 14 NNWT patients (divided between 7 patients from the geriatric unit and 7 from the spinal cord unit) is very small, and it is difficult to generalize to a larger Medicare-representative population based upon so few subjects. In addition, the device was used in conjunction with standard contact bandages, and as such does not parallel the method the requestor described as the typical way this device is to be used (i.e., as the primary bandage left on the wound at all times). Also it was interesting that the wound surface temperature increased with only the dome cover in place. This finding speaks to the need for a sham treatment group to help elucidate whether the benefit is from the noncontact chamber atmosphere created by the wound cover or from the active heating.

Price et al's article also had a number of methodologic flaws. First, there was no information on how subjects were recruited. Were the enrolled patients those who were consecutively seen at the investigation center? The method of patient selection is important to evaluate for any potential bias in their recruitment. A second serious problem with the study was the lack of information on the type of bed used, and general nursing care given, for both treatment and control groups. Making the groups as comparable as possible is important. If patients in one group received more intense or advanced ancillary care, this would bias the results in their favor. A final serious issue with the study's design was that data on all randomized patients was not analyzed. Only patients followed for a minimum of three weeks were included in the primary data analysis; eight patients dropped out before this three-week point with seven of the dropouts coming from the NNWT group. The authors did state that the data were re-analyzed using an intention to treat model. In this analysis none of the Kaplan Meier curves (i.e., time to 25, 50 or 75% of original wound area) were significantly different between the groups.

It is interesting that despite a bias to favor the treatment group, approximately the same number of patients in each group were healed completely at six weeks (2 controls and 3 NNWT subjects). Additionally, the number of non-healed ulcers was the same in each group (20 in both the NNWT and control subjects). Also of note was that neither the mean area of wound reduction nor the difference in pain was significantly different in either group. The authors performed a Kaplan Meier analysis to detect the time to reduction of wound area by 25%, 50% and 75%. They found that the time to a 25% and 50% reduction was shorter in the NNWT group. It is not clear if this was data taken from actual patient points or if it was extrapolated data. If it was from actual patient points, then the fact that mean area of wound reduction was no different in the groups suggests that while NNWT wounds might heal faster initially, by six weeks overall improvement is unchanged.

Three serious problems were noted in the design of the Whitney study. First was the method of patient selection. Using public service announcements to recruit patients introduces potential patient selection bias since self-referred subjects may not be representative of the pressure ulcer population. A second problematic issue was that the support surfaces used in the treatment and control groups were not comparable. Indeed, more control patients than NNWT patients used regular mattresses (8 controls vs. 4 NNWT) while more NNWT patients used air-powered support surfaces (9 NNWT vs. 5 controls). Using more advanced ancillary services in the treatment group potentially biases the outcome in their favor. A third concern was the high attrition rate. Of the 40 enrolled patients, six controls and five NNWT patients withdrew (11/40 or 27.5%). Withdrawals are always a potential problem. Nonetheless, it is incumbent upon the authors to prospectively address how subject attrition will be handled, and to include this in the discussion of their results. A final issue worth mentioning was that although wounds were assessed weekly, the rates of healing were expressed in cm/day. Thus, it appears that the weekly measurements were averaged over the intervening days; the validity of such an assumption should have been addressed.

In summary, the medical literature is not sufficient to support a positive national coverage determination on the use of NNWT for treating pressure ulcers. The three articles all suffer from small sample sizes and serious methodologic flaws. In addition, one study (Price 2000) demonstrated that the mean area of wound reduction at the end of their study was no different in the NNWT and control groups.

Venous Stasis Ulcers

Two studies (Cherry 1999 and Santilli 2000) investigated NNWT in venous ulcers. The study by Cherry suffered from two major problems. The first was its case-series design. As noted earlier, a comparison group is essential in order to draw make conclusions about a treatment's efficacy. In addition, this study included a change in two variables at the start of the study (introduction of NNWT and change in mode of compression stocking). It is notable that the four patients that healed in their 12-week follow-up all had the same compression bandage which was different from pre-study compressions. The one that did not heal had a different compression stocking. Thus, it is impossible to conclude that the healing resulted from the NNWT and not from the new type of compression bandage.

Santilli's study had numerous flaws. While using patients as their own controls is not, in and of itself, a major flaw, it was not clear from the study if the conventional wound care provided prior to NNWT was the same as that done during the warming therapy. Again comparability is a key issue. It is important when using patients as their own controls that the only difference after starting NNWT be the addition of the device, and not other changes in general wound care. In addition, the authors did not state how the patients in this study were selected (i.e. recruited) nor did they state what the total length of follow-up was. In the results section they mentioned a follow-up of 18 months for one group of patients, but it is unclear if this was the follow-up all subjects received. The baseline size of the lesions was very large (21.6 ± 45.8 cm²) again making comparability difficult. The study used the device for only two weeks but followed patients for an unstated time period. Prescribing a difference in healing rate to NNWT when the outcome occurred months down the line from warming treatment is of questionable validity. While not a design flaw, it is interesting to note their statement that a history of smoking or diabetes had no effect on wound healing in their patients. This runs contrary to general information on wound healing, and, while this may have been the result of small sample size and the population studied, the authors do not address this.

In summary, the medical literature is not sufficient to support a positive coverage determination on the use of NNWT for treating venous ulcers. The literature contains very small sample sizes with multiple serious study design flaws that make the validity of their results questionable.

Diabetic/Neuropathic Ulcers

The studies by Alvarez and McCulloch directly addressed the use of NNWT in diabetic ulcers. In addition, the requestor suggested that the study by Karr also be used to support this indication for NNWT. Karr's study, while it did include a majority of patients with diabetes, primarily looked at NNWT in ulcers overlying osteomyelitis. Thus, it cannot be used to assess NNWT for diabetic wounds.

Alvarez's study had some of the fewest major problems of any of the reviewed articles. They investigated 10 patients with diabetic foot ulcers receiving NNWT and 10 patients receiving conventional care. This was a randomized controlled trial with a 12-week follow-up. While the NNWT treated wounds showed a faster rate of healing than controls at every measurement point, the difference was never statistically significant. Thus, while the trend may appear to be faster healing for NNWT treated subjects, this would not be concluded. The study's major methodologic flaw was the lack of detail on how patients were selected (i.e., recruited). Also, the investigators stated that there were no significant differences in patient characteristics at baseline, but p values for these differences were not provided.

Although McCulloch et al stated their study was randomized, their method of randomization was problematic; they decided the initial patient's treatment based on a coin toss and subsequent patients were assigned treatment groups in an alternating fashion. The main result of randomization is to ensure that the treatment group assignments are not predictable. If one knows that the next enrolled patient will be placed in the opposite treatment group, and if there is any bias (overt or covert) on the part of the investigator enrolling subjects, then it is possible that patient enrollment, and subsequent randomization, would be open to bias. Another serious flaw in the study's design was the failure to discuss at the outset how subject drop-out would be handled. There was 10% attrition rate in each group (2 from each group). It appears that the authors simply removed these patients from the analysis. This is another potential source of bias affecting the results. Another less serious issue was the statement that the NNWT wound cover could not be used in conjunction with the off-loading devices. This appears to be in conflict with Alvarez's study where the NNWT wound cover was used in conjunction with off-loading sandals, and it is also different from how the requestor described the product's use to CMS.

In summary, the medical literature is not sufficient to support a positive coverage determination on the use of NNWT for treating diabetic ulcers. As with pressure and venous ulcers, the reviewed articles suffer from serious methodologic flaws. In addition, one study (Alvarez, publication pending) reported that the rate of healing in NNWT treated ulcers was not statistically faster than in control ulcers.

Complicated/Non-Healing Surgical Wounds and Chronic Wounds

There was no published literature that directly investigated this device for these wound types. Indeed, these wound classifications are very broad. CMS is unable to conclude that this device has utility in such wounds without clinical evidence.

Chronic Wounds, Whether or Not Falling Into One of The Foregoing Categories

There was no published literature that directly investigated this device for these wound types. Indeed, these wound classifications are very broad. CMS is unable to conclude that this device has utility in such wounds without clinical evidence.

Summary of CMS Analysis

In summary, the medical literature does not support a finding that NNWT heals any wound type better than conventional treatment. While the submitted studies purport better healing, due to serious methodological weaknesses, inadequate controls, and a variety of biases, the improved outcomes could also easily disappear in a properly controlled randomized trial.

Furthermore, there is no reason why such a trial could not be readily performed. A trial that would best answer our coverage concerns would be one where there was randomization to three arms: (1) experimental arm which would receive NNWT; (2) experimental arm which would receive NNWT, but with the heating element turned off; and (3) control arm which would only receive conventional therapy. Conventional therapy should be standardized across all three arms as applicable. In addition, these studies should adhere to the characteristics of good clinical trials outlined above. We would be happy to work with the requestor in designing such a trial. In the meantime, if the requestor is aware of additional data or information that would answer the methodological flaws or questions raised in the above analysis, as always, this decision can be reconsidered.

DECISION:

Medicare has decided to issue a national noncoverage policy for all uses of noncontact normothermic wound therapy for the treatment of wounds, because the medical literature is not sufficient to support a national coverage determination.

It is our intention to publish a noncoverage policy in the Coverage Issues Manual.

1 Lazarus, Gerald S., Cooper, Diane M., Knighton, David R., et al. Definitions and Guidelines for Assessment of Wounds and Evaluation of Healing, Arch Dermatol/Vol 130, April 1994

2 Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment. FDA/CBER/CDRH/CDER Draft, June 2000

3 Lait M, 1998.

4 Ibid.

5 Silver FH, Wang MC, A review of the etiology and treatment of skin ulcers with wound dressings: comparison of the effects of occlusive and nonocclusive dressings. J. Long Term Eff Med Implants 1992;2(4):267-88.

6 Valk G, *et al.* 2001.

7 Ibid.

8 *FDA Guidance for Industry: Chronic Ulcer and Burn Wounds - Developing Products for Treatment* (June 2000).

9 For example, Egger M., Smith G.D., Altman DG (eds.), *Systematic Reviews in Health Care: Meta-Analysis in Context*. BMJ Publishing Group, 2001; Gray J.A.M., *Evidence-Based Healthcare: How to Make Health Policy and Management NCDs*. Churchill Livingstone, 1998; Mulrow C., Cook D. (eds.), *Systematic Reviews: Synthesis of Best Evidence for Health Care NCDs*. American College of Physicians, 1998.

10 Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment.

FDA/CBER/CDRH/CDER Draft, June 2000

11 Park, 1998

12 Park, accepted for publication in *Wounds*

13 Winter, 1962

14 Millington, 2000

15 Plattner, 2000

16 Kloth, 2000

17 Whitney, 2001

18 Rabkin, 1987

19 Air-fluidized beds used for treatment of pressure ulcers in the home environment. Health Care Technology Assessment. October 9, 2001. Prepared by ECRI for the US Agency for Healthcare Research and Quality, Rockville, MD.

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